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# An easy-to-machine electrochemical flow microreactor: Efficient isoindolinone synthesis and flow functionalization

#### Ana A. Folgueiras-Amador, Kai Philipps, Sébastien Guilbaud, Jarno Poelakker and Thomas Wirth\*

**Abstract:** Flow electrochemistry is an efficient methodology to generate radical intermediates. An electrochemical flow microreactor has been designed and manufactured to improve the efficiency of electrochemical flow reactions. With this device only little or no supporting electrolytes are needed, making processes less costly and enabling easier purification. This is demonstrated by the facile synthesis of amidyl radicals used in intramolecular hydroaminations to isoindolinones. The combination with inline mass spectrometry facilitates a much easier telescoping of chemical steps in a single flow process.

Over the past decades, organic electrosynthesis has become recognized as one of the methodologies to perform redox reactions in an efficient, straightforward and clean way. Anionic and cationic radical species can be formed from neutral organic molecules generating a wide variety of useful reactive intermediates.<sup>[1]</sup> Electrons as reagents can achieve oxidations and reductions by replacing toxic or dangerous oxidizing or reducing reagents. As less chemicals are necessary to perform the reaction, fewer side products are formed. These features have recently sparked attention in the development of equipment<sup>[2]</sup> and in advanced synthetic protocols for electrochemical reactions.<sup>[3]</sup>

Organic electrochemistry is a powerful method for organic synthesis, but there are also limitations for electrochemistry in batch processes. As common organic solvents have typically low conductivity, the use and subsequent removal of supporting electrolytes is necessary. The large distance between electrodes in batch processes leads to large current gradients. Continuous flow reactors can address some of these problems.<sup>[4]</sup> Small electrode distances avoid large current gradients and reactions can be performed with small amounts or even without addition of supporting electrolytes, although modification of electrode surfaces have also been investigated.<sup>[5]</sup> A high electrode surface-to-reactor volume ratio allows a much-improved mass transfer on the surface of the electrodes leading to milder reaction conditions and short reaction times.

Microreactors for continuous flow electrosynthesis have already been developed.<sup>[6]</sup> We have contributed to that development with an electrochemical microreactor with a very small inter-electrode gap (100 – 250  $\mu$ m), which was applied for the synthesis of diaryl iodonium salts, for the difluoro- and trifluoromethylation of electron-deficient alkenes and for the electrochemical deprotection of *iso*-nicotinyloxycarbonyl group from carbonates and thiocarbonates.<sup>[7]</sup> Here we describe the development of a much improved, second-generation electrochemical microreactor. This

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reactor can be made with an aluminum body (Figure 1b), or from polymers by using additive manufacturing technology (3D printing, Figure 1c). The latter offers the possibility for the reactor to be manufactured with lower cost within a few hours and also offers facile customization if needed according to the specifications of the reaction. The large electrode area (anode and cathode: 25 cm<sup>2</sup> each) with robust and secure electrodewire connection and easily exchangeable electrode materials leads to more flexibility, but also higher productivity and efficiency. The two electrodes are separated by a spacer of FEP (fluorinated ethylene propylene) foil, while the reaction solution is flowing through a channel cut out in the FEP foil (Figure 1d). Sealing is achieved through the FEP foil when the two electrode blocks are screwed together. The flow reactor is shown in Figure 1 and all details of its construction including files for additive manufacturing (3D printing) can be found in the supporting information. The distance between the electrodes is defined by the thickness of the FEP spacer (typically 100 – 500  $\mu$ m). A small distance between the electrodes is important and the use of supporting electrolytes often superfluous.



Figure 1: Electrochemical flow reactor. a) Schematic diagram; b) Aluminum reactor; c) Reactor made by additive manufacturing through monomer polymerization; d) FEP spacer with flow channel.

Nitrogen-containing heterocycles are very important components in drugs and bioactive natural products. Their synthesis has been explored with different methodologies, many of them involving the use of precious transition metals or toxic reagents.<sup>[8]</sup> Using the above-described electrochemical flow reactor, we use here an alternative method for the synthesis of *N*-heterocycles via a nitrogen-centered radical accessed through electrochemical oxidation and its subsequent addition to alkenes in an intramolecular cyclization. Such *N*-centered radicals have already been used in batch electrochemical processes.<sup>[9]</sup>



Scheme 1. Electrochemical cyclization of carbamate 1.

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With the cyclization of carbamate **1** to product **2** (Scheme 1), general conditions for the electrochemical reaction were explored such as electrode materials, solvents and bases. In batch reactions, where NBu<sub>4</sub>BF<sub>4</sub> (0.1 M) is used as supporting electrolyte, different electrode materials were investigated to explore the reactivity.

With platinum as cathode, the reaction behaved very similar with almost any electrode material used as anode. But the results are very different when the cathode is not platinum. Only 1 F mol<sup>-1</sup> of electricity is theoretically needed for the one-electron oxidation, but even with 4 F mol<sup>-1</sup> the reaction did not go to completion in most cases (see supporting information for details). The counter electrode (cathode) clearly has a larger impact on the reaction than the working electrode (anode). This is due to the water reduction reaction taking place at the cathode (see proposed mechanism in Scheme 2), and the different activation overpotential for hydrogen evolution on different electrode materials.<sup>[10]</sup> The activation overpotential is lower for platinum (-0.07 V) than for nickel (-0.28 V), and much higher for graphite (-0.62 V) (all vs Ag/AgCl). As the results obtained for graphite, platinum and boron doped diamond (BDD) as anode are very similar, graphite was used as the most inexpensive material.

The reaction from 1 to 2 was carried out in different solvents and solvent mixtures, such as acetonitrile, methanol, 1,1,1,3,3,3hexafluoroisopropyl alcohol (HFIP) and water, and it was found that acetonitrile/water mixture is the optimum solvent mixture for this reaction. Although HFIP is known to be efficient for stabilizing cations and radicals,<sup>[11]</sup> it led to either recovery of starting material (< 2 F mol<sup>-1</sup>) or decomposition (> 3 F mol<sup>-1</sup>). The use of a base can be favourable in anodic oxidations if the compound or its oxidized form can be deprotonated as most anodic oxidations undergo loss of electrons and protons.<sup>[9b,12]</sup> Xu et al.<sup>[9]</sup> reported the cyclization of carbamates of type 1 in batch using lithium hydroxide or sodium carbonate as a heterogeneous base. The drawback of these bases is their low solubility in organic solvents which is clearly more problematic for flow than for batch processes. Different organic bases were investigated in the flow cyclizations (see supporting information), but triethylamine inhibited the reaction while with 2,6-lutidine similar conversions as without base was observed. This was explained by measuring the cyclic voltammogram of substrate 1 in the presence of different bases (see supporting information). The oxidation potential of triethylamine is much lower than of 1, so it will be oxidized first, and the starting material remains unreacted.



Scheme 2. Proposed mechanism.<sup>[9]</sup>

The oxidation potential of **1** after addition of 2,6-lutidine remains practically unchanged, which explains the similar result with and without base. The mechanism proposed by Xu *et al.*<sup>[9]</sup> (Scheme 2) shows that the cathode-generated hydroxide anion assists in the deprotonation of the carbamate before forming the nitrogen radical. With sodium carbonate as base the reaction proceeded to completion after 3 F mol<sup>-1</sup>, but the amount of water had to be increased (50% in acetonitrile) in order to dissolve the base. This led to poor solubility of the product in the solvent mixture and to precipitation and blocking of the flow system after 10 minutes of operation, making this base/solvent system inefficient for continuous flow.

To accelerate the reaction, benzyltrimethylammonium hydroxide **6** was used. Full conversion of **1** after 3 F mol<sup>-1</sup> was achieved and **6** as soluble base was used in further optimization studies. Cyclic voltammetry endorses this result, as the cyclic voltammogram in the presence of benzyltrimethylammonium hydroxide shows a lower oxidation potential (from 1.74 V to 0.27 V, vs Ag/AgCl). This second oxidation potential corresponds to the deprotonated form of compound **1**, which will facilitate the production of the radical at the anode (see supporting information). Moeller and co-workers have observed comparable results where deprotonated sulfonamides exhibit a lower oxidation potential than the neutral compounds.<sup>[13]</sup> We also found that under the optimized reaction conditions the thickness of the spacer can be varied from 250 µm to 500 µm with no change in the reaction yield.

The optimized conditions were then applied to the synthesis of isoindolinones in flow. Such isoindolinone motifs are found in many natural products, pharmaceuticals and biologically active molecules (Figure 2).<sup>[14]</sup>



Figure 2. Biologically active isoindolinone derivatives.

The cyclization of amide **7** to isoindolinone **8** was investigated in detail. For this purpose, the electrochemical reactor was connected to an inline mass spectrometer, which allowed a rapid assessment of the required amount of electrons. As shown in Figure 3, at least  $3 \text{ F mol}^{-1}$  is necessary in order to achieve full conversion. Only 0.5 equivalents of the base are needed to complete the reaction, but with smaller amount of the base full



Scheme 3. Cyclization of amide 7 to 8 with MS analysis.

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conversion cannot be achieved. Here the base can be considered as an electrolyte, but with much lower loadings than electrolytes in batch electrochemical reactions and can be removed easily through aqueous work-up.

With the optimized reaction conditions (3 F / mol<sup>-1</sup>, 24 mA, 1-2 V) in hand, different substrates were examined as shown in Figure 4. While aromatic moieties on the amide nitrogen are required to stabilize the nitrogen radical, the substituents on the alkene moiety can be varied widely.



Figure 3. Inline mass spectrometric analysis of the electrochemical flow reaction  $7 \rightarrow 8.$ 

Only with the 4-OMe functionality present in the aromatic ring next to the double bond, the reaction results in a complex mixture leading to a low yield of the desired products (15 and 16). Due to the radical pathway of the cyclization, the diastereoselectivities are low and were dictated only by steric effects. The stereochemistry of the substrate was also found not to affect the selectivity, thus when pure E- or Z-isomers are used for the reaction the same diastereomeric ratios are obtained for compound **12**. The (R,S)/(S,R) diastereomer is always favored as confirmed by X-ray crystallographic analysis of compound 12 (see supporting information).<sup>[15]</sup> When electron-withdrawing substituents such as chloride are attached to the aromatic ring adjacent to the double bond, the reduced product 20 is observed in addition to 19. Such reduced compounds are the only products with a 3-nitrophenyl substituent (21 and 22), where no TEMPO addition is observed. In these reactions no gas evolution is observed, which implies that there is no gaseous hydrogen formed from proton reduction. Since TEMPO is not being consumed here as is not added to the final product, the redox cycle can be completed by reducing the oxoammonium cation to the free radical. A flow reaction on slightly larger scale



Figure 4. Substrate Scope for the cyclization reaction.

was performed for 1.5 h leading to **12** in 96% yield (180 mg). The same reaction performed in batch required supporting electrolyte and provided product **12** after 6 h in only 51% yield (107 mg). This also demonstrates the efficiency of the flow process allowing a supporting electrolyte-free electrochemical reaction.

A tandem cyclization reaction was then attempted with a vinylphenyl substituent on the nitrogen, but only monocyclized product **18** was obtained (Scheme 4). This compound now bears a functionalized styrene moiety which could be used in subsequent reactions. NMR characterization of **18** was difficult due to the appearance of broad peaks, which could only be slightly improved at high temperature NMR. After separation of the diastereomers, the oxygen – nitrogen bond was cleaved with zinc and acetic acid and the structures of the two diastereoisomers **23a** and **23b** were determined by X-ray analysis (see supporting information).<sup>[15]</sup>



Scheme 4. N–O-bond cleavage of compound 18.

The isoindolinone products were then used for subsequent functionalization, including elimination of the TEMPO moiety and reduction of the nitrogen-oxygen bond. The elimination reaction was performed using the same base as used in the cyclization to yield alkenes such as **24**,<sup>[16]</sup> which can be employed in further reactions. Furthermore, the electrochemical cyclization and the elimination were coupled in a single flow system as shown in Scheme 5.



Scheme 5. Two-step flow reaction: cyclization and elimination. BPR: back pressure regulator.

In order to achieve full conversion to compound **24**, the reaction conditions were investigated and a residence time of 25 minutes at 85 °C / 2.8 bar were found to be optimal (see supporting information, Table S2). Compound **24** was obtained as a mixture of *E*- and *Z*-isomers, with excess of the *E*-isomer (up to 9:1 in entry 6 for compound **24**, and up to 19:1 for compounds **25** and

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**26**). The configuration was determined by NOE NMR (see supporting information).

The nitrogen-oxygen bond reduction in flow was performed using a Zn cartridge<sup>[17]</sup> and acetic acid, as shown in Scheme 6.<sup>[18]</sup> The cartridge was heated to 40 °C to achieve full conversion to the corresponding alcohols (Scheme 6). Compounds **30–32** were prepared in 54–80% overall yield.



Scheme 6. Two-step flow reaction: cyclization and reduction.

Two additional transformations performed in the electrochemical flow reactor without supporting electrolyte are shown in Scheme 7. The electrolysis of thioacetic acid generates the corresponding radical. Unlike carboxylic acids, which decarboxylate and react in Kolbe reactions, the thioacetyl radical is stable and adds smoothly to terminal alkynes to yield products such as **33**. The use of hexafluoroisopropanol (HFIP) to stabilize the formed radical is crucial as with other solvents dimerization of thioacetic acid is observed. An intramolecular C–H thiolation of *N*-arylthioamides to form benzothiazoles such as **34** can also be performed with superior yields than the batch process, which needs TEMPO and a supporting electrolyte to operate.<sup>[19]</sup>



Scheme 7. a) Electrochemical addition of thioacetic acid to phenyl acetylene; b) Electrochemical C–H thiolation of an *N*-arylthioamide to benzothiazole **34**.

In conclusion, a new and efficient flow electrochemical microreactor has been designed and manufactured which was used to generate nitrogen and sulfur-based radical intermediates for syntheses with no or little supporting electrolyte. In addition, one of the first combinations of an electrochemical reaction with a second one in a single flow system is demonstrated.<sup>[20]</sup>

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**Keywords**: flow electrochemistry • cyclizations • isoindolinones • microreactors • tandem reactions

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None or little supporting electrolyte needed in flow electrochemistry: Recycling and waste problems are eliminated as cyclization products are obtained in a fast and clean process.



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